

### REMARKS

Prior to entry of the present amendment, claims 2-7, 10, 11, and 13-24 are pending. Claim 20 is rejected under 35 U.S.C. § 112, second paragraph, claims 2-3, 6-7, 11, 13-18, and 23-24 are rejected under 35 U.S.C. § 102, and claims 2-7, 10-11, 13-14, 15-19, and 21-24 are rejected under 35 U.S.C. § 103. Claims 11, 13-19, and 24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting. Applicants address each basis for rejection as follows.

#### Claim amendments

Claims 2 and 20 have been amended for consistency. New claims 25-29 have been added. Claim 25 finds support, for example, at page 8, lines 1-3, of the English language specification. New claims 26 and 27 find support, for example, at page 10, lines 6-7, of the English language specification. New claims 28 and 29 find support, for example, at page 10, lines 16-20, of the English language specification. No new matter has been added by the present amendments.

Applicants reserve the right to pursue any cancelled subject matter in this or in a continuing application.

#### Rejection under 35 U.S.C. § 112, second paragraph

Claim 20 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in depending from cancelled claim 1. Claim 20 has been amended to depend from claim 2. The indefiniteness rejection may be withdrawn.

#### Rejection under 35 U.S.C. § 102

Claims 2-3, 6-7, 11, 13-18, and 23-24 are rejected under 35 U.S.C. 102(a) as being anticipated by Shibata et al. (The 10<sup>th</sup> Annual Meeting 2004, August 05-06, Poster 088). The Office states that “Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in

accordance with 37 CFR 1.55.”

To perfect the priority claim to JP 2003-374808 (filed November 4, 2003) and JP 2004-187028 (filed June 24, 2004), enclosed herewith are English language translations of these applications. The Japanese priority applications were filed prior to the August 2004 date of the Shibata reference and provide support for the presently claimed invention (see, e.g., the claims of JP 2003-374808, as well as page 6, lines 20-24, and page 8, line 22, to page 9, line 15 of the English language translation of JP 2003-374808). Applicants submit that Shibata is not available as prior art under 35 U.S.C. § 102(a) against the presently claimed invention. This basis for rejection should be withdrawn.

#### Rejection under 35 U.S.C. § 103

Claims 2-7, 10-11, 13-19, and 21-24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Song et al. (US 2002/0123479 A1; “Song”) in view of Tokusumi et al. (US 6,746,860; “Tokusumi”), Jin et al. (Gene Therapy 10:272-277, 2003; “Jin”), Hwu et al (US 6,734,014; “Hwu”), and Waller et al (US 2005/0013810; “Waller”). Applicants respectfully disagree.

The determination whether an invention would have been obvious under 35 U.S.C. § 103 is a legal conclusion based on underlying findings of fact. *In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000). The factual determinations underpinning the legal conclusion of obviousness include 1) the scope and content of the prior art, 2) the level of ordinary skill in the art, 3) the differences between the claimed invention and the prior art, and 4) evidence of secondary factors, also known as objective indicia of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). In *KSR Int’l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007), the Supreme Court reasserts the “Graham factors” as the correct legal standard and notes:

The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.

*Id.* at 1739. Applicants submit that the results obtained by the claimed methods were not predictable based on the cited art.

*Discussion of the Cited References*

The Office states (page 6 of the Office Action, 1<sup>st</sup> full paragraph; emphasis original):

Song et al did not teach explicitly the use of a Sendai virus vector for genetically modifying immature dendritic cells such as dendritic progenitor cells, even though they disclosed that dendritic cells, including dendritic progenitor cells could be genetically modified by any recombinant negative strand RNA virus including any paramyxovirus.

Applicants note that the disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. (M.P.E.P. § 2121.01 citing *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003)).

In the above-cited passage from the Office Action, the Office asserts that Song disclosed that any recombinant negative strand RNA virus could be used for genetic modification of dendritic cells and its progenitor cells. However, Song only provides results of gene introduction into dendritic cells using a retrovirus vector. Applicants submit that one skilled in the art, based on Song, would not reasonably conclude that any recombinant negative strand RNA virus could be used without undue experimentation because no working example using a virus vector other than a retrovirus vector is provided. The mere recitation of language in a reference does not mean that the subject matter described by the language is necessarily enabled by the disclosure. The Office has shown no reasonable explanation why Song enables use of any recombinant negative strand RNA virus, much less Sendai virus, for genetic modification of dendritic cells or its precursors. Applicants submit that Song does not enable the scope of disclosure that the Office relies on in making the present obviousness rejection.

The Office further states (page 6 of the Office Action, 2<sup>nd</sup> full paragraph; emphasis original):

Tokusumi et al already disclosed the preparation of at least a recombinant Sendai virus vector to be used for transfer of foreign genes (see at least the abstract as well as Summary of the Invention). Tokusumi et al further disclosed that the Sendai virus vector is useful for gene therapy due to its safety, high gene transfer efficiency and capacity to express a foreign gene in a high level.

Applicants note that Tokusumi merely shows a working example using LLC-MK2 cells which are an established cell line derived from kidney epithelial cells of a macaque monkeys. The Office provides no explanation as to why the disclosure of Tokusumi is also applicable to immature dendritic cells or precursors of immature dendritic cells to generate the results disclosed in the present application that are the basis for the presently claimed invention. The Office fails to establish that the presently claimed methods were predictable based on the cited art.

The Office also states (pages 6-7 of the Office Action; emphasis original):

Additionally, Jin et al already disclosed successfully a method in which recombinant Sendai virus was in contact and provided a highly efficient gene transfer into human cord blood CD34+ cells, including human cord blood HSCs and more immature cord blood progenitor cells (see at least the abstract; page 276, col. 1, last paragraph).

Although Jin teaches the gene transfer of Sendai virus into CD34+ cells, Jin does not teach or suggest the successful differentiation of CD34+ cells containing Sendai virus into mature dendritic cells. As demonstrated in Applicants' specification, Sendai virus infection can change the cell state. Namely, immature dendritic cells infected with Sendai virus undergo spontaneous maturation without further maturation stimulus. Applicants submit that, prior to the present invention, there was no reasonable expectation that Sendai virus could be transduced into CD34+ cells without disturbing differentiation of the cells into dendritic cells, maturation of dendritic cells, or the function of mature dendritic cells (e.g., in antigen presentation to T cells).

Applicants, in the present specification, demonstrated that Sendai virus transduction into dendritic cell precursor cells does not disturb their successive differentiation into immature dendritic cells (see, e.g., page 46, lines 9-26, Experiment 6).

The present specification also demonstrates that immature dendritic cells transduced with Sendai virus spontaneously differentiate into mature dendritic cells (see, e.g., page 46, line 30, to page 47, line 3). The present specification further demonstrates that mature dendritic cells generated by transduction with Sendai virus successfully induced a potent allogenic T cell response (see, e.g., Figure 21), and suppressed tumor growth (see, e.g., Figures 21 and 23). All of these data indicate that the gene transduction with Sendai virus vector into a dendritic cell or its precursor causes no apparent adverse effects on the dendritic cell differentiation and function, but rather brings a surprising beneficial effect. The Office has failed to establish that these results were predictable before the present invention.

Further, Applicants submit that the Office's argument based on Jin does not apply to new claims 26-29, which recite CD11c<sup>+</sup> cells.

In addition, the Office states (page 7 of the Office Action, 1<sup>st</sup> full paragraph; emphasis original):

Moreover, Hwu et al also taught at least a method of preparing recombinant dendritic cells by transforming a hematopoietic stem cell, including CD34+ cells derived from a variety of sources such as cord blood, bone marrow and mobilized peripheral blood, with a nucleic acid followed by differentiation of the stem cell into dendritic cells in the presence of GM-CSF, TNF-alpha and optionally together with IL-4 (see at least the abstract; col. 9, lines 29-57; col. 10, line 60 continues to line 13 of col. 11; col. 15, lines 15-46).

Applicants submit that Hwu merely provides experimental data using retrovirus vectors. The experiments disclosed in Hwu are similar to those of Cremer described in Applicants' last response. As mentioned above, experiments using retrovirus vector do not provide a reasonable expectation of success of the gene transfer of Sendai virus vector into dendritic cells. Furthermore, Applicants submit that the results shown in the present

application, namely that gene transduction with a Sendai virus vector into a dendritic cell or its precursor causes no apparent adverse effects on dendritic cell differentiation and function, but rather brings a surprising beneficial effect, is unexpected over the disclosure of Hwu. Hwu does not remedy the lack of predictability described above of arriving at the presently claimed invention.

The Office also states (page 7 of the Office Action, 2<sup>nd</sup> full paragraph; emphasis original):

Furthermore, Waller et al also taught that progenitors of dendritic cells can be identified in many tissues, such as bone marrow and blood, based on the expression of certain cell surface markers; and that dendritic cell progenitors are typically identified by the expression of one or more of the following markers on its cell surface CD11c, CD13, CD14, CD33, CD34 or CD4 (see at least paragraphs 24-28 and 36).

Applicants submit that Waller merely describes gene markers of dendritic cell progenitors. Again, Applicants submit that, for the reasons stated above, Waller fails to remedy the lack of predictability of the presently claimed invention.

#### *Argument in Reply to the Office Action*

In response to Applicants' last reply, the Office states (pages 9-10 of the Office Action; emphasis original):

Firstly, the above rejection is made under 35 U.S.C. 103(a) and therefore there is no requirement that the primary Song et al reference has to teach the use of a Sendai virus vector, let alone demonstrating specifically transfection of a precursor of a dendritic cell (e.g., CD34 cells) with a Sendai virus vector. Nevertheless, Song et al taught specifically compositions and methods useful for stimulating an immune response against one or more disease associated antigens, including cancer associated antigens, by genetically modifying dendritic cells including dendritic progenitor cells, *in vivo* or *ex vivo*, wherein the dendritic cells were genetically modified by a recombinant negative strand RNA virus (e.g., vesicular stomatitis virus, paramyxoviruses, orthomyxoviruse[s] and

bunyaviruses) directing the expression of at least one disease associated antigen.

Applicants agree that there is no requirement that the primary Song reference has to teach the use of a Sendai virus vector since the rejection is made under 35 U.S.C. § 103(a). Clearly, other references can be combined with Song. However, Applicants note that, a *prima facie* case of obviousness can only be established if one of ordinary skill in the art would have had a reasonable expectation of success in making the proposed modification or combination (M.P.E.P. § 2143.02). The Office, for the reasons explained below, has failed to meet this burden.

The Office asserts that Song taught compositions and methods, wherein the dendritic cells were genetically modified by a recombinant negative strand RNA virus (e.g., vesicular stomatitis virus, paramyxoviruses, orthomyxoviruses and bunyaviruses). However, as stated above, Applicants submit that Song does not enable the full scope of this disclosure, but rather is limited to introduction of a retrovirus vector into dendritic cells. Therefore, it is inappropriate to rely on Song's mere mention of negative strand RNA viruses in rejecting the presently claimed invention. Moreover, Song does not teach or suggest the unexpected result of the invention, namely that gene transduction with Sendai virus vector into a dendritic cell or its precursor causes no apparent adverse effects on dendritic cell differentiation and function, but rather brings a surprising beneficial effect. This result is unpredictable over Song.

The Office further states (page 10 of the Office Action; emphasis original):

Thirdly, in contrast to Applicant's position that highly efficient gene transduction to immature dendritic cells or dendritic precursor cells such as CD34 stem cells by Sendai virus vector was unpredictable at the effective filing date of the present application, **the teachings of Jin et al cited in the above rejection indicated otherwise.** It is further noted that the Jin et al reference was applied as a 102(b) reference to previously unamended claim 2 in the Office action dated 6/5/08. Furthermore, Li et al (J. Virol. 74:6564-6569, 2000; IDS) also demonstrated that **Sendai virus vector mediated a gene transfer and expression in various types of animal and human cells, including non-dividing cells, with high efficiency** (see at least the

abstract).

As the Office states, Jin teaches the gene transduction of CD34+ cells with Sendai virus vector. However, Applicants respectfully note that CD34+ cells infected with Sendai virus are not a claimed subject matter. The claims encompass methods for producing a mature dendritic cell. These methods require contacting a Sendai virus vector with an immature dendritic cell (e.g., a CD34+ cell) or contacting a Sendai virus vector with a precursor of a dendritic cell and differentiating the precursor cell into an immature dendritic cell, where the immature dendritic cell undergoes maturation, thereby producing a mature dendritic cell. The claimed invention as a whole must be considered when determining obviousness (see M.P.E.P. § 2141.02 citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983)).

The specification demonstrates that Sendai virus vector does not disturb any step of the differentiation of hematopoietic progenitor CD34+ cells into mature dendritic cells. This result was surprising. Applicants found that Sendai virus vector infection surprisingly did not disturb subsequent differentiation, and, also surprisingly, changed the maturation state of dendritic cells without the need for stimulation (e.g., by incubation with bacteria, lipopolysaccharide, or double-stranded RNA (see, e.g., Figures 8 and 9 of the specification)). The Office has failed to establish that a person of ordinary skill in the art would have been able to predict that use of a Sendai virus vector would not disrupt the differentiation of immature dendritic cells into mature dendritic cells.

On this point, Applicants also note that the specification demonstrates that dendritic cells differentiated from CD34+ cells still express the transgene of Sendai virus vector at a very high level (see, e.g., Figures 11 and 12 of the specification). CD34+ cells are hematopoietic progenitor cells and dendritic cells are terminally differentiated cells, both are very different from each other. The specification demonstrates that neither a significant reduction of the transgene expression nor vector elimination occurred during the process of differentiation from CD34+ cells into mature dendritic cells. Applicants submit that these results are unpredictable and surprising.



The Office further relies on Li for teaching that Sendai virus vector mediated gene transfer and expression in various types of animal and human cells, including non-dividing cells, with high efficiency. It is true that Li demonstrates the gene transduction into several types of cells including primary neuron culture and rat brain (Figures 5 and 6 of Li). However, Applicants submit that the disclosure of Li is insufficient to reasonably predict that Sendai virus vector can transfer the target gene into any cell type with high efficiency. In fact, Applicants have shown that the infectivity of Sendai virus to mature dendritic cells was low as argued in Applicants' last response (Experiment 4, Fig. 9(B)). Applicants submit that Li, like the other references, does not render the presently claimed methods of producing a mature dendritic cell obvious because Li, even if combined with the other cited references, does not establish that one of ordinary skill in the art would have had a reasonable expectation of success in carrying out the claimed method.

Applicants submit that the teachings of Li are irrelevant to new claims 26-29 which recite a CD11c<sup>+</sup> cell and not a CD34<sup>+</sup> cell.

The Office further states (page 10 of the Office Action, last line):

Fourthly, the instant claims do not require any particular transfection efficiency.

In response, Applicants note that transfection efficiency is a result which is a necessary outcome when the claimed invention is carried out. Applicants respectfully point out that disclosed inherent properties are part of "as a whole" inquiry. In determining whether the invention as a whole would have been obvious under 35 U.S.C. § 103, the office personnel must first delineate the invention as a whole. In delineating the invention as a whole, the office personnel looks not only to the subject matter which is literally recited in the claim in question... *but also to those properties of the subject matter which are inherent in the subject matter and are disclosed in the specification* (See M.P.E.P. § 2141.02(V)). As such, comments made by Applicants concerning transfection efficiency are relevant even if the claims do not require a particular efficiency.

With respect to the spontaneous maturation described in the present specification

and encompassed by the present claims, the Office states (page 11 of the Office Action; emphasis original):

Firstly, please refer to the combined teachings ... of Song et al., Tokusumi et al., Jin et al., Hwu et al and Waller et al, particularly Jin et al already disclosed successfully at least a method in which recombinant Sendai virus was in contact and provided a highly efficient gene transfer into human cord blood CD34+ cells, including human cord blood HSCs and more immature cord blood progenitor cells.

As an initial matter, in reference to the above section discussing transfection efficiency, Applicants agree that Jin teaches use of Sendai virus for gene transduction into CD34+ cells. However, as also argued above, the differentiation of dendritic precursor cells into immature dendritic cells or spontaneous maturation of immature dendritic cells into mature dendritic cells after contacting with a Sendai virus are neither an inherent feature nor necessary outcome of the CD34+ cells taught by Jin<sup>1</sup>. These unexpected features of the invention must be considered when determining obviousness.

The Office also states (page 11 of the Office Action):

Secondly, please note that the methods and compositions resulted from the combined teachings of Song et al., Tokusumi et al., Jin et al., Hwu et al and Waller et al are indistinguishable from the methods and compositions as claimed by the present application.

As noted above, Applicants submit that the results shown in the present application, namely that gene transduction with Sendai virus vector into a dendritic cell or its precursor causes no apparent adverse effects on dendritic cell differentiation and function, but rather brings a surprising beneficial effect, is unexpected. It is this unexpected result that is encompassed by the claimed methods. The unexpected result, which is neither taught nor suggested in the cited art, and was not even inherently present, should be taken in consideration because an unexpected result is an evidentiary factor of obviousness (See

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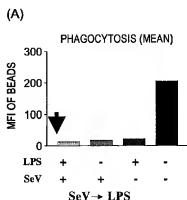
<sup>1</sup> To emphasize this point, claim 2 has been amended to recite "~~to cause~~ and differentiating the precursor cell ~~to differentiate~~ into an immature dendritic cell."

M.P.E.P. § 716.02(a)( I) and (II)).

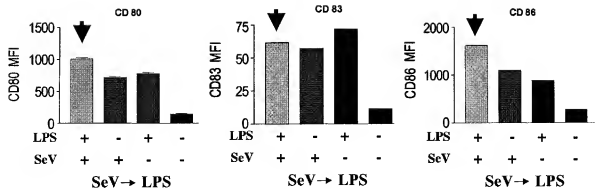
The Office further states (page 11 of the Office Action):

Thirdly, please also note the open language of the term “comprises” in the method claims, indicating that at least the claimed methods encompass any stimulation steps if desired.

It is true that claims do not exclude stimulation steps to mature dendritic cells. However, as long as an immature dendritic cell carries a Sendai virus vector, spontaneous maturation is triggered. No other stimulation is required. Moreover, even if other stimulation were given to dendritic cells, it cannot be concluded that the spontaneous maturation does not occur. The specification provides experimental data showing the result of further stimulation in addition to the infection with the Sendai virus. It was known that lipopolysaccharide (LPS) induces maturation of immature dendritic cells. When immature dendritic cells were subjected to both Sendai virus and LPS, phagocytosis (a hallmark of immature phenotype of dendritic cells) was suppressed stronger than when stimulated by either virus or LPS alone (see Figure 17 (A) of the specification; reproduced below; arrow inserted).



High-level expression of maturation marker genes (CD80, CD83, and CD86) as a whole suggests an advantage of using Sendai virus in addition to LPS (see Figures 14 and 15 of the specification; reproduced below; arrows inserted).



Accordingly, stimulation in addition to use of Sendai virus may have an additional beneficial effect. The additional stimulation does not, however, replace the effect seen with Sendai virus alone. The presently claimed invention is directed to method of producing mature dendritic cells that requires nothing more than contacting immature dendritic cells or precursors of dendritic cells with Sendai virus and differentiating the precursor cells into immature dendritic cells. Contacting with Sendai virus in the absence of additional stimulation is sufficient to produce a mature dendritic cell. While use of the term “comprises” in the claims allows for additional steps, the fact that the method works without these additional steps is surprising and unpredictable over the cited art. Use of the term “comprising” does not negate the nonobviousness of the presently claimed methods.

Applicants submit that this basis for rejection is not applicable to new claim 25 which excludes further stimulation for maturation.

Finally, Applicants address the Office’s comments regarding the Cremer reference cited in the previous reply. The Office states (page 10 of the Office Action):

Secondly, the reference to the Cremer et al article in the IDS is irrelevant. Cremer et al did not teach or suggest the use of a Sendai virus for genetically engineering any cell, including CD34+ stem cells.

And states (page 12 of the Office Action):

Fourthly, once again the reference to the Cremer et al is irrelevant because it was not used in any rejection in this Office action or in the previous

Office action dated 6/5/08. Moreover, the Cremer et al reference teaches exclusively the use of a retroviral vector without any suggestion on the use of a recombinant negative strand RNA virus (e.g., vesicular stomatitis virus, paramyxoviruses, orthomyxoviruses and bunyaviruses), let alone a Sendai virus vector.

Applicants submit that Cremer is referred to as relevant to the state of the art at the time of filing of the present application. The Cremer reference provides additional evidence in relation to the disclosure of the Song reference relied on by the Office. The Cremer reference should not be analyzed in isolation. As discussed above, retrovirus vectors were used in the working example of Song. Applicants submit that the Cremer reference is relevant to what one skilled in the art would expect if the retrovirus vector of Song were used for a gene transfer to dendritic cells. The fact that the results obtained using the presently claimed method are superior to those described by Cremer, as explained in the last reply, in turn suggests that the presently claimed methods are superior the working example of Song.

Moreover, as further evidence that Song would not suggest to one skilled in the art to use a Sendai virus vector, Applicants note that Song expressly indicates that a recombinant retroviral vector is a “preferred embodiment” (see paragraph [0052] of Song).

For all the above reasons, Applicants submit that the presently claimed invention is nonobvious over the cited art. The rejection under 35 U.S.C. § 103 should be withdrawn.

#### Provisional Obviousness-Type Double Patenting

Claims 11, 13-19, and 24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1, 3-6, and 8-14 of co-pending application serial number 11/630,532 (“the ‘532 application”).

M.P.E.P. § 804 states:

If “provisional” ODP [obviousness-type double patenting] rejections in two applications are the only rejections remaining in those applications, the

examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer.

Applicants note that the present application, filed May 3, 2006, is the U.S. national stage of a PCT international application filed on October 29, 2004, whereas the ‘532 application, filed December 21, 2006, is the U.S. national stage of a PCT international application filed on April 28, 2005. Applicants submit that the present application, relative to the ‘532 application, is the earlier filed application. As such, if the provisional obviousness-type double patenting rejection is the last remaining rejection in the present case, Applicants respectfully request that this provisional rejection be withdrawn and the application allowed to issue.

CONCLUSION

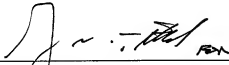
Applicants submit that the application is now in condition for allowance, and such action is hereby respectfully requested.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Clark & Elbing LLP  
101 Federal Street  
Boston, MA 02110  
Telephone: 617-428-0200  
Facsimile: 617-428-7045

  
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James D. DeCamp, Ph.D.  
Reg. No. 43,580  
  
John A. Titterton, Ph.D.  
Reg. No. 52,210